Current use and utility of magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and pancreatic duct stents: A secondary analysis from the Western Trauma Association multicenter trials group on pancreatic injuries

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INTRODUCTION: The single most important predictor of pancreas-specific complications (PSCs) after pancreatic trauma is injury to the main pancreatic duct (MPD). Pancreatography has been recommended to evaluate the integrity of the MPD. In addition, pancreatic duct stents have been proposed to prevent or treat PSC. The primary purpose of this study was to determine the accuracy of magnetic resonance cholangiopancreatography (MRCP) in diagnosing MPD injury. We further sought to determine whether stents were effective in preventing PSC or facilitated the resolution of pancreatic leaks or fistulae.

METHODS: A secondary analysis of a multicenter retrospective review of pancreatic injuries in patients 15 years and older from 2010 to 2018, focusing on patients who underwent MRCP or endoscopic retrograde cholangiopancreatography (ERCP), was performed. Final pancreatic injury grade was determined based on all available assessments, ultimately adjudicated by the site principal investigator. Data were analyzed using various statistical tests where appropriate.

RESULTS: Thirty-three centers reported on 1,243 patients. A total of 216 underwent pancreatography—137 had MRCP and 115 ERCP, with 36 having both. The sensitivity of MRCP for MPD injury was 37%, the specificity was 94%, the positive predictive value was 77%, and the negative predictive value was 73%. When compared with ERCP, MRCP findings were discordant in 64% of cases. Pancreatic stents were placed in 77 patients; 48 (62%) were to treat PSC, with no clear benefit. Twenty-nine had prophylactic stents placed. There did not appear to be benefit in reduced PSC compared with the entire study group or among patients with high-grade pancreatic injuries.

CONCLUSION: The accuracy of MRCP to evaluate the integrity of the MPD does not appear to be superior to computed tomography scan. Consequently, the results of MRCP should be interpreted with caution. The current data do not support prophylactic use of pancreatic stents; they should be studied in a prospective trial. (*J Trauma Acute Care Surg.* 2023;95: 719–725. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Pancreas; pancreatography; MRCP; ERCP; stents.

Traumatic pancreatic injury remains a challenge, and it frequently requires multidisciplinary care and prolonged follow-up.[1–3] Individual patient outcomes after pancreatic injury are dependent on multiple factors such as age, preexisting medical conditions, physiology at presentation, and synchronous injuries.[4–9] Mortality is rarely attributable to the pancreatic injury itself, but pancreas-specific complications (PSCs) such as pancreatic leak, peripancreatic abscess, pancreatic fistula, or delayed pancreatic pseudocyst are a major cause of morbidity. A recent Western Trauma Association (WTA) multicenter trial found that the mechanism of injury, primary management strategy, and annual trauma center pancreatic injury volume were all predictors of PSC.[7–9] However, the single most important risk factor for PSC, as has been known for decades, is main pancreatic duct (MPD) injury.[7–18]

The identification of MPD injury has long been a conundrum.[10–12,14,16,19,20] Approximately half of patients with pancreatic trauma are taken directly to the operating room

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without advanced imaging, and the diagnosis of pancreatic injury is made intraoperatively.[7,9] The criteria for MPD injury described by Heitsch et al.[10] in 1976 have proven useful in guiding contemporary management.[15,21] Among the other half of patients, whose pancreatic injury is identified by computed tomography (CT), the ability to reliably ascertain MPD integrity is suboptimal.[7,9,19,20] Consequently, recent guidelines have recommended magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) when the diagnosis remains uncertain.[22–24] Endoscopic interventions to treat and prevent PSC have been recommended by a number of authors,[25–30] and endoscopic treatment of PSC was included in the original WTA algorithm for the management of pancreatic trauma.[22] One of the original aims of the WTA multicenter trial was to evaluate recent trends in the use of MRCP and ERCP, as well as endoscopic placement of pancreatic duct stents to either prevent or treat PSC.

The primary purpose of this study was to determine the accuracy of MRCP in diagnosing MPD injury. We further sought to determine whether stents were effective in preventing PSC or facilitated the resolution of pancreatic leaks or fistulae. We hypothesized that MRCP is equivalent to CT in identification of MPD injury and that stents do not reduce the occurrence of PSC.

PATIENTS AND METHODS

This study represents a secondary analysis of a retrospective, multicenter, multinational study of traumatic pancreatic injuries conducted under the auspices of the WTA Multicenter Trials Committee.[7–9] Inclusion criteria were 15 years or older, American Association for the Surgery of Trauma Organ Injury Scale[31] grades I to V pancreatic injury, direct admission to participating American College of Surgeons–verified (or locally designated, in foreign countries) levels I and II trauma centers between January 2010 and September 2018. Patients who were transferred from other hospitals after laparotomy or specific pancreatic intervention were excluded; those who died within 24 hours were included for demographic reporting but were excluded from outcomes analyses. For the purpose of this study, we focused on those patients who underwent MRCP or ERCP.

Data Collection

This study was conducted following approval from the appropriate institutional review board at each collaborating center with a waiver of informed consent and STrengthening the Reporting of OBservational studies in Epidemiology checklist was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/C999).[32] Each site provided deidentified data for patients with pancreatic injuries included in the institution's trauma registry. The case report form included demographic information and detailed data regarding injuries, diagnostic testing, interventions, and outcomes. The timing and specific findings of imaging studies, operative and endoscopic interventions, and decision making were recorded. The primary outcome of interest was PSC. Outcomes were recorded for the index hospitalization and up to 30 days after discharge.

The case report form requested information about pancreatic injury grade based on CT and intraoperative inspection, where performed. The case report form also requested additional information about MRCP and ERCP/stent findings if these studies were performed. The final pancreatic injury grade was assigned by the site principal investigator at each center. In any cases of discrepancy or uncertainty based on all of the available information on the case report forms, the coordinating center contacted the site principal investigator to discuss and determine the final grade. This final pancreatic injury grade was used for all outcome analyses in the study. Indications for ERCP and stenting were recorded as either prophylactic or for treatment of a PSC.

Statistical Analysis

Patient demographics and characteristics are reported using descriptive statistics, including mean, median, interquartile range, and proportions. Continuous variables were compared using *t* test; for not normally distributed data, Wilcoxon rank-sum test was performed. The χ^2 test, Fisher's exact test, two-proportion *z* test, or one-proportion *z* test was used to compare categorical variables. Missing data did not exceed 10%, so no adjustment to address missingness was made. Statistical significance was defined as p value of <0.05. All statistical tests were performed using R software (version 4.2.0; The R Foundation, Vienna, Austria).

RESULTS

Patients

Thirty-three trauma centers (31 level I, 2 level II) from the United States, Canada, Australia, and Israel provided complete data on 1,243 patients. Of those, 1,110 survived 24 hours and were analyzed for management and outcomes. Pancreatography was performed in 216 patients (19% of all 24-hour survivors): 137 had MRCP and 115 underwent ERCP (12% and 10% of 24-hour survivors, respectively), with 36 patients (3% of 24-hour survivors) having both MRCP and ERCP. Of those who underwent ERCP, 77 (67%) had endoscopic stents placed. No patient in this study was reported to have undergone intraoperative pancreatography.

Diagnostic Utility of MRCP

An MRCP was performed in 137 patients, at a median time of 30.7 hours (IQR, 16.6–171.7 hours) after injury. To assess the accuracy of MRCP in determining MPD injury, we excluded eight patients in whom MRCP was performed after pancreatic resection, as the site of injury was removed. The comparisons between MRCP reading and the final pancreatic injury grade are summarized in Table 1. The finding of "major duct leak," consistent with high-grade pancreatic injury (HGPI; American Association for the Surgery of Trauma Organ Injury Scale[31] grades III–V), was reported in 22 patients. Of these, 5 (23%) had low-grade pancreatic injury (LGPI; grades I and II). "Minor duct leak," consistent with LGPI, was reported in nine patients, of whom four (44%) were ultimately found to have HGPI. One MRCP was called "inconclusive" in a patient with grade IV injury. There was "no duct leak," consistent with LGPI, on 97 MRCPs, but 24 (25%) of those patients were determined to have HGPI. The sensitivity of MRCP for significant pancreatic ductal injury was 37%, the specificity was 94%, the positive predictive value was 77%, and the negative predictive value was 73%. In all, 95 of 129 (74%) of MRCP were accurate with regard to the final injury grade, but of 46 patients with HGPI, MRCP

TABLE 1. Magnetic Resonance Cholangiopancreatography Results and Injury Grades

	Final Pancreatic Injury Grade						
MRCP Reading	**I**	**II**	**III**	**IV**	**V**	**n (%)**	**MRCP/Injury Grade Discordance, n (%)**
Major duct leak	1	4	14	1	2	22 (17%)	5 (23%)
Minor duct leak	3	2	3	1	0	9 (7%)	4 (44%)
No duct leak	24	49	17	3	4	97 (75%)	24 (25%)
Inconclusive	0	0	0	1	0	1 (1%)	1 (100%)
Subtotals, n (%)	28 (22%)	55 (43%)	34 (26%)	6 (5%)	6 (5%)	Total = 129 (100%)	34 (26%)
MRCP/injury grade discordance, n (%)	1 (4%)	4 (7%)	20 (59%)	5 (83%)	4 (67%)	34 (26%)	

Boxes outlined in bold border indicates MRCP findings considered discordant from final injury grade. Shaded areas indicate HGPI.

showed a major duct leak in only 17 (33%). Among the 29 patients who had HGPI missed on MRCP, 19 (66%) suffered PSC.

There were 36 patients who had both MRCP and ERCP; a comparison of their readings is shown in Table 2. Ten (28%) of the patients had MRCP readings consistent with HGPI, but three (30%) of them had no duct injury seen on ERCP. Of the 26 without major duct leak seen on MRCP, 16 (62%) had a major duct leak on ERCP. There were seven other patients with discordant findings on ERCP when compared with MRCP. One patient had inconclusive results with both tests. Overall, the two tests were discordant in 64% of cases. In 17 (47%) of cases, it was discordant to the degree that would change the management. Based on these data, the sensitivity of MRCP for significant pancreatic ductal injury was 30%, the specificity was 75%, the positive predictive value was 70%, and the negative predictive value was 36%.

Diagnostic ERCP and Therapeutic Stents

An ERCP was performed in 115 patients, at a median of 115.2 hours (IQR, 42.2–354.2 hours) after injury. Thirty-eight patients (33%) had diagnostic ERCP only, and 77 (67%) had stents placed. The indication for the stent was for treatment of a PSC in 48 patients (62% of stent patients), and these were placed at a median of 220.9 hours (IQR, 102.8–457.1 hours) after injury. Prophylactic stents were placed in 29 patients (38%) at a median of 54.5 hours (IQR, 29.5–173.9 hours) ($p < 0.01$ compared with timing of treatment stents). Data regarding the exact positioning of the stent were incomplete. Because there were no notations of stents traversing MPD disruptions, it is presumed that the stents were transpapillary stents positioned to decompress the pancreatic duct. A breakdown of ERCP and stent placement by injury grade is detailed in Table 3.

Among patients with LGPI, 49 had ERCP performed—24 (49%) were diagnostic only, and 25 (51%) received stents. In patients with grade I injuries, nine had stents to treat PCs (one after resection, eight after surgical peripancreatic drain placement), while four had prophylactic stents along with surgical drainage. There were six patients with grade II injuries who had stents placed to treat PCs, all after surgical treatment. Two of them had pancreatic resections, and four had nonresectional surgery (peripancreatic drain placement or other pancreatic procedure such as debridement or suturing, without resection or drain placement). Another six patients with grade II injuries had prophylactic stents placed—two in the setting of nonoperative management (NOM) and four after nonresectional surgery.

There were 66 patients with HGPI who underwent ERCP, and 52 had stents placed (Table 3). Thirty-five patients with grade III injuries received stents. Twenty were placed to treat PSC—10 after resection, 9 after nonresectional surgery, and 1 during NOM. Fifteen were placed prophylactically—five after resection, eight after nonresectional surgery, and two during NOM. A total of 17 patients with grade IV and V injuries had stents placed. Four of them were prophylactic, and 13 were to treat PSC (4 after resection and 9 after nonresectional surgery).

Stent Outcomes

The prophylactic efficacy of stents was assessed based on the occurrence of PSC among patients who had prophylactic stents placed (n = 29), compared with the occurrence of PSC among patients who did not have prophylactic stents. A variety

TABLE 2. Magnetic Resonance Cholangiopancreatography and ERCP Findings

	ERCP Findings					
MRCP Reading	**Major Duct Leak**	**Minor Duct Leak**	**No Duct Leak**	**Inconclusive**	**Subtotals**	**MRCP/ERCP Discordance, n (%)**
Major duct leak	7	0	3	0	10	3 (30%)
Minor duct leak	2	0	2	0	4	4 (100%)
No duct leak	14	2	5	0	21	16 (76%)
Inconclusive	0	0	0	1	1	0 (0%)
Subtotals	23	2	10	1	Total = 36	23 (64%)
MRCP/ERCP discordance, n (%)	16 (70%)	2 (100%)	5 (50%)	0 (0%)	23 (64%)	

Boxes outlined in bold border indicates MRCP findings considered discordant from ERCP findings. Shaded areas indicate HGPI.

of comparisons were performed (Table 4). The group receiving prophylactic stents was compared with the entire study population that survived 24 hours and did not have prophylactic stents placed, the subgroup of pancreatography patients (MRCP and ERCP) who had no prophylactic stent, and the subset of patients who underwent ERCP and had no stent placed (Table 4). Overall, patients who had prophylactic stents had significantly higher rates of PSC (48%) compared with those who had no prophylactic stent (28%, $p = 0.02$). Looking specifically at those with HGPI, who are theoretically most likely to benefit from a prophylactic stent, PSC occurred in 63% of those who had a prophylactic stent versus 41% of the 24-hour survivors who did not have a prophylactic stent ($p = 0.053$). There was no subset that we analyzed that appeared to benefit from prophylactic stents.

To evaluate the benefit of stents in treating PCs, the hospital length of stay (LOS) was compared between patients with PCs who had a stent placed versus those with PCs who did not have a stent. The median LOS was 31 days (IQR, 18–48 days) among those who had a stent versus 23 days (IQR, 14–38 days) among those without a stent ($p = 0.047$).

DISCUSSION

The recent WTA multicenter trial on pancreatic injuries has reinforced that injury to the MPD is the most critical factor in determining the risk of PSC and in guiding management. Consequently, there is a very high value placed in the accurate determination of the integrity of the MPD.

Because approximately one-half of patients have their pancreatic injury diagnosed intraoperatively,[7,9] it is important for the surgeon to recognize signs of MPD injury. Intraoperative criteria for ductal injury as described by Heitsch et al.[10] include direct visualization of duct injury, complete pancreatic transection, laceration through more than half the diameter of the pancreas, central pancreatic perforation, or severe maceration of the pancreas. The Memphis group[15,21] has promoted a management algorithm based on these criteria, with lower morbidity among patients appropriately selected for nonresectional management. With visual inspection alone, there remains the possibility of MPD injuries being either missed or overtreated. While intraoperative pancreatography was emphasized in the 1970s and 1980s,[11,12,14,33] its utility in the current era has been questioned.[34,35] Schellenberg et al.[35] reported a series of patients who were managed operatively, relying on visual inspection alone in 94%. Among those who had intraoperative pancreatography via cholecystotomy or duodenotomy, all were inconclusive. Intraoperative pancreatography was not reported in any patients in the WTA study, and we do not endorse its routine use. On the other hand, intraoperative ultrasonography is a tool with which surgeons have become increasingly comfortable, and a direct assessment of the MPD may prove beneficial in directing optimal treatment.[36] This is worthy of trauma surgeon education and further assessment of accuracy. If intraoperative evaluation is inconclusive, peripancreatic drainage is encouraged and postoperative pancreatography may be considered.

Most stable patients with abdominal trauma will undergo CT scanning. Advances in cross-sectional imaging have limited, but not eliminated, the need for pancreatography. However, given the inaccuracy of CT in evaluating MPD integrity,[5,9,19,20] pancreatography still seems to have an indication. A role for ERCP in trauma was first proposed in 1976 by Gougeon et al.,[37] and ERCP remains the criterion standard for assessment of pancreatic duct integrity. Pancreaticographic classification of ductal injuries appears to be a useful tool in selecting patients for NOM and in planning interventions.[38–40] However, because ERCP is invasive and can be difficult to orchestrate on short notice and after-hours, noninvasive imaging with MRCP has been recommended as first-line imaging.[22–24]

In 1999, Nirula et al.[41] first described the use of MRCP in trauma, and a later case series of 10 patients reported 100% clinical utility, identifying pancreatic duct injuries in 4 patients and excluding it in 6.[42] However, the accuracy of MRCP has been called into question. A recent multicenter study from Japan[43] reported sensitivity and specificity of MRCP for MPD injury to be 80% and 89%, respectively. Although these numbers seem reasonable, MRCP was inferior to ERCP and no better than CT in their institution. In a multicenter study from the pediatric Pancreatic Trauma Study Group, Rosenfeld et al.[44] found that MRCP confirmed duct integrity in only 62% of patients and was not superior to CT. Aydelotte et al.[45] reported just 80% sensitivity and

TABLE 3. ERCP and/or Stent Placement for Management of Pancreatic Injury

	Final Pancreatic Injury Grade					
	I	II	III	IV	V	n (%)
ERCP only	5	19	11	2	1	38 (33%)
ERCP + stent	13	12	35	12	5	77 (67%)
Totals	18 (16%)	31 (27%)	46 (40%)	14 (12%)	6 (5%)	115 (100%)

	Final Pancreatic Injury Grade					
Reason for Stent	I	II	III	IV	V	n (%)
Prophylaxis	4	6	15	2	2	29 (38%)
Treat PSC	9	6	20	10	3	48 (62%)
Subtotal stents	13 (17%)	12 (16%)	35 (46%)	12 (16%)	5 (7%)	77 (100%)

Shaded areas indicate HGPI.

TABLE 4. Impact of Prophylactic Stent Use on PSCs

	n	PSC	p
Overall			
Prophylactic stent	29	14 (48%)	—
All 24-h survivors who did not have prophylactic stent	1,081	306 (28%)	0.02
All pancreatography (MRCP + ERCP) patients who did not have prophylactic stent	187	95 (51%)	0.80
All ERCP patients who did not have any stent	38	20 (53%)	0.72
HGPIs			
HGPI, prophylactic stent	19	12 (63%)	—
HGPI, 24-h survivors who did not have prophylactic stent	407	166 (41%)	0.053
HGPI, pancreatography (MRCP + ERCP) patients who did not have prophylactic stent	73	54 (74%)	0.35
HGPI, ERCP patients who did not have any stent	14	9 (64%)	0.94

p Value represents comparison with prophylactic stent PSC.

54% negative predictive value for MRCP in the evaluation of choledocholithiasis, biliary duct masses and strictures, and pancreatic duct abnormalities. In the current study, the overall accuracy of MRCP was 74%, with a marked difference between LGPI (94%) and HGPI (33%) subgroups. Among 36 patients who had both MRCP and ERCP, there was discordance between the MRCP and ERCP readings in 64% of cases. Of 23 patients with a major duct leak seen on ERCP, only 7 (30%) were identified as such on MRCP. With these considerations, the utility of MRCP for determining MPD integrity is questioned. At best, the results of MRCP should be interpreted with caution. If MRCP findings seem discordant with the clinical picture or CT findings, we recommend further evaluation with close observation, ERCP, or operative exploration as appropriate.

Based on success in healing pancreatic duct disruptions in various pancreatic disorders, endoscopic stenting has been used to manage traumatic MPD disruptions and posttraumatic PSC.[25–27,29,30] Pancreatic sphincterotomy or stent placement can eliminate the 30 to 40 mm Hg pancreatic duct sphincter pressure gradient and allow unimpeded forward flow of pancreatic juice into the duodenum, but there have been very few studies reporting outcomes. Rogers et al.[26] reported on five patients who had sphincterotomy or stents for PSC, all of whom had resolution without further interventions. However, they did not report the time to resolution. Bhasin et al.[27] reported 75% success (three of four) in managing fistulae nonoperatively with stents or nasopancreatic drain. Thomson et al.[29] reported on a series of 48 patients who had ERCP after pancreatic trauma. Pancreatic fistula was found in 25, of whom 12 had sphincterotomy, and 6 received a stent. All were reported to have resolved without surgical intervention, but further details are lacking.

In the current series, 62% of stents were placed to treat PSC. While theoretically beneficial, the current study design and limitations in data collection do not allow definitive determination of the efficacy of this treatment. We observed a longer LOS among patients with PSC who had a stent placed, compared with those with PSC who did not have a stent. No conclusions can be drawn from this; it will require prospective study with robust data collection. While it has been suggested that stents be placed to traverse the site of disruption, there is significant variation in the size, positioning, timing, and duration of stents.[38,40] We do not have specific data on the positioning of the stents in this study. It may be that specific stent positioning makes a difference and that will need to be studied.

Twenty-nine patients received stents prophylactically, to attempt to avoid PSC. This practice, while theoretically reasonable, is supported by limited data. Kong et al.[28] reported a reduction in PSC (26% vs. 46%) and improved success of NOM (91% vs. 70%) with endoscopic placement of pancreatic stents or nasopancreatic drains; the benefit was seen in patients with grades II and III injuries. Kim et al.[30] used ERCP to diagnose MPD injury and treated 21 patients operatively, 15 with stents and 7 with neither intervention. The PSC rate in the three groups was 76%, 67%, and 71%, respectively. The current study was not powered or designed to specifically determine the efficacy of pancreatic duct stenting. Among various comparisons, including those looking specifically at patients with HGPI, we found no indication that PSCs were decreased by the placement of a prophylactic stent. In fact, in some comparisons, the stents appear to be associated with an increase in PSC. It is important to note that, given the selection bias and inconsistency in stent placement, as well as the lack of information on decision making, there is no single comparison that we consider scientifically sound. All we can say with certainty is that this intervention needs to be studied prospectively. This is made more important by the recognition that there can be complications from stent placement. Kim et al.[30] and Bhasin et al.[38] both mention a concerning association of early pancreatic stenting with pancreatic duct strictures. Further caution comes from a prospective multicenter cohort study of 2,808 ERCP procedures, of which 92% were therapeutic. They reported complications in 11.6% of patients and a procedure-related mortality of 1.4%.[46] In the absence of clear clinical benefit, we urge caution in prophylactic endoscopic stenting outside a clinical trial.

Limitations

This study was retrospective in design and suffers from all the limitations of such studies. The most significant limitation was that this was a secondary analysis of a study that was not originally designed to specifically determine the accuracy of MRCP or efficacy of pancreatic duct stents. There were inadequate data to determine the specific findings of ERCP and details on stents. Estimation of the prophylactic and therapeutic efficacy of stents is compromised by selection bias and inconsistency in the clinical use of stents, as well as the lack of information on decision making. Injury grading may have been inaccurate because CT scanning, intraoperative assessment, and MRCP all have shortcomings. Management may have been influenced by factors other than the injury grade and imaging findings, and our ability to determine clinical decision making was limited. The recording of PSC was based on retrospective review rather than prospective documentation with strict definitions; consequently, a pancreatic leak or fistula may have been diagnosed based on an arbitrary decision to measure pancreatic enzymes in drain fluid. Furthermore, we did not have data on the consequences of each specific PSC (e.g., interventions, contribution to LOS). Data may not be representative of worldwide management because the majority was collected from academic centers with WTA members. However, a broad range of centers is represented, so these data and the conclusions should be generalizable. The study period ended in October 2018, so more recent data are not included, and it is possible that ongoing evolution in care is occurring.

CONCLUSION

The accuracy of MRCP to evaluate the integrity of the MPD does not appear to be superior to CT scan, and only 33% of HGPIs were identified correctly on MRCP. The utility of MRCP is questioned, and its results should be interpreted with caution, particularly if committing to major pancreatic resection or to NOM of a significant pancreatic injury. If there is a need to clearly delineate the ductal anatomy, ERCP is preferred. The accuracy of MRCP should be studied in a prospective controlled clinical trial.

Regarding pancreatic stents, the current data do not support their prophylactic use. Whether stents help in the resolution of pancreatic leak or fistula warrants further study in a controlled

trial with standardized definitions of PSC and rigorous data collection, including longer-term outcomes. The results of the WTA multicenter trial may be useful in informing the design of future clinical trials, including power analysis.

AUTHORSHIP

W.L.B., C.G.B., E.E.M., and M.C. contributed in the study concept and design. All authors contributed to the acquisition of data. W.L.B. and M.C. contributed in the statistical analysis. W.L.B., C.G.B., E.E.M., M.W., R.M.R., Z.J.B., and L.K. and M.C. contributed in the interpretation of the data and drafting of the article. All authors contributed in the critical revision of the article for important intellectual content, and all authors approved the final version of the article.

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The authors declared no conflicts of interest.

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